DOCKET 98N-1215

Comments on Proposed Rule "Foreign Establishment Registration and Listing" as published in the FEDERAL REGISTER OF MAY 14, 1999

(comments by July 28, 1999)

Page 26331. Section 207.3 - Definitions. I note that manufacturers of biologics, particularly foreign firms, have in the past not realized that biologics meet the definition of drugs under the FD&C Act and are required to meet (most, e.g., 21 CFR 211) of the same requirements as "drug" manufacturers. I would suggest that this section specifically clarify that foreign biologics manufacturers are required to register and to list their products. This same concern applies to manufacturers of biologic devices licensed by the Center for Biologics Evaluation and Research (CBER)

Also, CBER allows licensing of "bulk drug substances" for further manufacture. These sites are licensed and inspected on a regular basis. CBER allows licensing arrangements for short supply, divided, shared, and contract manufacturing arrangements. CBER published a document on "Cooperative Manufacturing" in the FEDERAL REGISTER of November 25, 1992 detailing the requirements with regard to registration. However, that document did not specifically address who was responsible for the registration process (i.e., the license holder of the final product versus the establishment owner of the "bulk drug substance").

This proposed rule allows for reporting by "affiliate companies" and there is "joint ownership and control." I believe it would clarify for manufacturers, as well as FDA personnel, what "affiliate companies" are (are they partnerships such as in cooperative manufacturing scenarios or are they companies that own the production company) and when "joint ownership and control" (joint ownership and control of the product or of the manufacturing site?) is applicable under "Cooperative manufacturing." I believe the simplest and easiest manner to deal with these problems of definition is to require that if a biologic intermediate is licensed, it is required to be listed and the production site to be registered, and that this is the responsibility of the license holder (license holder of the intermediate for "bulk drug substances" and license holder of the final drug for final drug products).

For example, under the definition under proposed 207.3, it states in part, "...except that the term shall not include distribution of any drug that is neither imported nor offered for import into the United States." This appears to contradict the November 25, 1992 Cooperative Manufacturing policy, in that a foreign "bulk drug substance" supplier, who is selling (?distributing?) such a substance "for further manufacture" to a foreign biologics manufacturer, who would than finish and ship the product to the United States, would not be required to register. Is this a correct interpretation of the definition? And is it what FDA intends? I note that the "bulk drug substance" supplier in this example is licensed by CBER and regularly inspected. The product in this example, "for further manufacture" will be processed at an overseas site, and will than be shipped to the United States for distribution in the US.

Also, the current policy with regard to biologic source suppliers (e.g., allergenic source suppliers) should be clarified, i.e., are they required to be registered?

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Section 207.25. Does this section apply to the number assigned to a BLA (Biologics License Application)?

Section 207.37. I note that the current procedures for examining drug registration listings are cumbersome and inconvenient. FDA should strive, as stated in the Reinventing Government initiatives, to make it's processes transparent and it's procedures readily available. I would suggest that this information (I presume it is public) be posted on the internet. In addition to making it available to interested parties on a timely basis, it would also do much to assure that the information is correct and current (assuming FDA develops a SOP on who to contact to correct errors and which agency entity is responsible for making corrections).

Page 26332, Section 207.21 - Times for Registration and Drug Listing. This section does not address (for biologics) manufacturing sites that are currently licensed but not registered. When would FDA expect these sites to register?

Page 26336, Section 807.20 - Who Must Register and Submit a Device List. Although I am not familiar with an actual example as I am with "bulk drug substances" for further manufacturing use, the same scenario could arise. For example, there is a manufacturer that produces a "component" of a biologic in-vitro test kit (this "component" is integral to the performance of this in-vitro test kit). The "component" is licensed and was inspected prior to approval. The component is shipped to the US for further manufacture, i.e., incorporation into a in-vitro test kit. In this case, would FDA expect the foreign component supplier to register (and list)?

Page 26338, E. *Registration Schedules* This section states that part 207 applies to "...some biologics..." Could FDA clarify which biologics it applies to (or which biologics it does not apply to) and the rationale for including or excluding a biologic?

Page 26343, Subpart B, 807.20 This section gives the definition of the term device as "...in vitro diagnostic biological products not subject to licensing under section 351 of the Public Health Service Act."
Are devices licensed under section 351 of the Public Health Service Act required to be listed and registered or are devices licensed under section 351 exempt?

Signed

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